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Docket No. 02P-0191. **Response by Teva Pharmaceuticals USA To**
Additional Comments of R.W. Johnson PRI and Ortho-McNeil Pharmaceutical Inc.

In its various submissions to this docket, Ortho-McNeil Pharmaceuticals ("McNeil"), the sponsor and marketer of Ultram® brand tramadol hydrochloride tablets (tramadol), has raised a plethora of irrelevant, misleading, and contradictory arguments, none of which have changed the fact, as demonstrated in Teva's Petition, that Teva's labeling:

- √ **Complies with the regulatory "same labeling" requirement,**
- √ **Fully protects McNeil's exclusivity, and**
- √ **Does not render Teva's drug unsafe for the uses for which it is labeled.**

Accordingly, Teva's tramadol ANDA is eligible for, and must receive, immediate final approval. The following comments respond in order to the arguments raised in McNeil's May 31, 2002 comments.

I. TEVA IS ENTITLED TO CARVE OUT THE EXCLUSIVE TITRATION DOSING REGIMEN FOR CHRONIC PAIN

McNeil argument: Labeling Teva's tramadol for "patients for whom rapid onset of analgesic effect is necessary and for whom the benefits outweigh the risks...would necessarily omit all of the information regarding Ortho-McNeil's studies that provide the necessary context to evaluate what risk would be incurred and, therefore, make it impossible to determine who would qualify as a member of the 'subset'" of patients for whom Teva's drug will be labeled. McNeil 5/31 Comments at 2.

Response: McNeil's titration studies and the titration dosing regimen do not bear any relation to "what risk would be incurred" with non-titration dosing. This is because:

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(1) titration dosing is never a permissible option for patients with pain requiring rapid onset of analgesic effect, and thus patients requiring rapid onset of analgesic effect are not a subset of patients who do not require rapid analgesic effect;

(2) the risks and benefits to be considered for non-titration dosing are the benefit of immediate dosing, and the risk of immediate dosing. These risks and benefits were both fully established long before McNeil's 25 mg titration study, which only measured discontinuation rates (not risks), and only compared discontinuation rates between a 16-day titration schedule and a 10-day titration schedule. *See* Ultram Labeling, Titration Trials section. In other words, McNeil's study provided no information whatsoever about the non-titrated dosing schedule and is irrelevant to the safe use of Teva's tramadol product. Therefore, the omission of the exclusive 25 mg titration dosing information from Teva's labeling is safe and appropriate.

> **McNeil argument**: "[T]he two dosing schemes set forth in the current Ultram label are to be used depending on the intensity of the pain, not duration." McNeil 5/31 Comments at 2.

Response: This position ignores the inherent temporal meaning of the terms "chronic" and "rapid" by suggesting that they bear no relation to duration of pain or required speed of relief. McNeil's position would require FDA to redefine the term "chronic," to mean only "moderate," yet McNeil itself contradicts this position by pointing out that the titration dosing regimen is permitted for both "moderate [and] moderately severe *chronic* pain." It is logically and grammatically nonsensical, and contrary to FDA's findings, for McNeil to suggest that the dosing regimens are not intended to differentiate the chronic or acute nature of the pain.

> **McNeil argument**: Although "Ultram is currently indicated for patients with moderate to moderately severe pain, whether that pain is acute or chronic," "the Ultram labeling does not adopt treatment of acute pain as a distinct therapeutic use of the product." McNeil 5/31 Comments at 2.

Response: Acute pain patients may never use the titration dosing schedule because it is only recommended for patients who do not require rapid pain relief. *See* Teva 5/23 Comments at 3-5. Thus, as FDA properly found, the Ultram labeling *does* recognize treatment and dosing for acute pain. *See* FDA Medical Team Leader Review Memorandum, December 20, 1999, discussed in Teva's May 23 response at 3 ("The applicant [i.e., McNeil] also proposed making changes [to] the Dosage and Administration section to describe the dose titration for chronic pain before, rather than after, the description of dosing for acute pain.").[1] Accordingly, the only reasonable conclusion FDA can reach now is that acute pain is distinctly provided for in the non-titration dosing instructions of the Ultram and Teva labeling.

> **McNeil argument**: Teva's proposed labeling "would still include patients with chronic pain, who may need the rapid onset of analgesic effect that Teva's proposed dosing would address." McNeil 5/31 Comments at 2.

[1] www.fda.gov/ohrms/dockets/dailys/01/Oct01/102501/cp00001.pdf, at 75, 77.

Response: McNeil offers no evidence that physicians would in fact adopt this construction of the non-titration dosing schedule. However, as Teva pointed out in its original petition,

> even if the Ultram statement of use for "patients for whom rapid onset of analgesic effect is required" could be semantically construed to include certain types of chronic pain requiring rapid relief, the fact would remain that Teva's labeling safely excludes all patients for whom the 25 mg titration dosing regimen is recommended. Teva Petition at 5.

As Teva further explained in its Petition and its May 23 comments, the inherent safety of Teva's proposed labeling is due to the fact that any patient who requires rapid pain relief, whether for acute or chronic pain, cannot be dosed with the titration dosing schedule, because titration dosing is reserved for patients "not requiring rapid onset of analgesic effect."

II. TEVA'S LABELING IS SAFE FOR THE CONDITIONS OF USE OF TEVA'S DRUG, AND MCNEIL'S EXCLUSIVITY CANNOT COVER TREATMENT OF ACUTE PAIN

McNeil argument: Teva's labeling would result in a product "less safe than Ultram." McNeil 5/31 Comments at 3-4.

Response: McNeil mischaracterizes the regulatory test for exclusivity labeling carve-outs. The proper test is whether the generic product would be safe for use under the conditions prescribed, recommended, or suggested ***in the generic product's labeling***.[2] Teva's labeling only includes the use of tramadol for patients requiring rapid pain relief – i.e., for whom non-titration dosing is required – and for those patients Teva's labeling is the same as Ultram's labeling. Because this group of patients is never eligible for titration dosing, Teva's labeling is equally safe as Ultram's for the conditions of use that are actually in the Teva labeling.

McNeil argument: Ultram's indication statement "would sweep in all treatment of moderate to moderately severe pain – without limitation to acute pain. There would be no instructions in the [Teva] labeling about how to use the product for most patients coming within the approved indication....As a result, Teva's proposed labeling would clearly be less safe than Ultram's." McNeil 5/31 Comments at 3.

Response: Neither Ultram nor Teva's tramadol may be dosed for patients requiring rapid onset of analgesic effect using the titration dosing schedule because it will not provide rapid pain relief. Thus for these patients physicians will have no choice but to dose Ultram and Teva's tramadol in exactly the same manner – without titration. *See* Teva 5/23 Comments at 4-6. Because the Teva and Ultram labeling is identical for these patients, they are clearly equally safe. For patients who are eligible for the exclusive titration dosing, the only way doctors can prescribe Teva's tramadol is by disregarding the fact that Teva's product is only labeled for pain requiring rapid onset of relief. As shown in Teva's 5/23 Comments at 5, FDA may not and should not base drug approval decisions on the assumption that doctors will violate the drug's labeling.

[2] *See* 21 U.S.C. §§ 355(j)(5)(D)(iv), 355(j)(2)(A)(v), and 21 C.F.R. § 314.94(a)(8)(iv); *see also, Zeneca v. Shalala*, 1999 U.S. Dist. LEXIS 12327 at 31-34 (D. Md. Aug. 11, 1999), *affirmed* 216 F.3d 161 (4th Cir. 2000).

Nevertheless, McNeil persists in urging FDA to consider off-label use as a basis to deny Teva's approval because, as McNeil now alleges, Ultram's indication "sweep[s] in all treatment of moderate to moderately severe pain" and Teva's label must therefore provide instruction for "all treatment of moderate to moderately severe pain." However, McNeil's interpretation of the Ultram indication is incorrect and overbroad because its clinical trials specifically excluded patients with many types of moderate to moderately severe pain, including: trigeminal neuralgia; post-herpetic neuralgia; pain from myocardial infarction; pain from tempomandibular joint syndrome; pain from thrombophlebitis; and chronic painful conditions solely related to dysmennorhea or recurrent headache. *See* Ultram NDA 20-281 Supp. 016, Medical Officer Review, Feb. 23, 1999.[3] The absurdity of McNeil's position is that it would require withdrawal of Ultram's approval due to the lack of data and instructions for treating those types of pain. However, because tramadol has been studied in, approved, and labeled for use in acute pain using non-titrated dosing (as reflected in Teva's labeling), Teva's omission of a different condition of use – treatment of chronic pain using titration dosing – in no way permits or requires FDA to refuse to approve Teva's ANDA.

> **McNeil argument**: Teva's labeling "would seriously mislead practitioners who cannot know that the adverse events of nausea and vomiting can also be reduced through titration." McNeil 5/31 Comments at 4.

Response: This is incorrect and irrelevant because for patients requiring rapid onset of pain relief, titration dosing is never an option. Moreover, McNeil's argument is a serious misrepresentation because the Ultram titration studies and labeling do not support a reduction in the adverse events of nausea and vomiting, but rather only state that the 25 mg titration schedule "resulted in fewer discontinuations due to nausea or vomiting." There is no evidence in the Ultram labeling that the titration schedule reduced the side effects themselves, and even if that were the case, the gastrointestinal nuisance effects of nausea and vomiting, which are common and expected with all opioid pain relievers, are not serious enough to constitute approval-blocking "safety" concerns under FDA's regulations.

> **McNeil argument**: Because the phrase "and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses" "was added to the label as part of Ortho-McNeil's labeling supplement...and refers directly to the results of research conducted by Ortho-McNeil in support of its approval,...the underlined language is entitled to the same three-year exclusivity" as the titration dosing schedule.

Response: The underlined phrase is not eligible for exclusivity because it does not refer in any way to the clinical trials that supported approval of the titration dosing schedule. Rather, the word "benefits" refers to the benefits of immediate full dosing, which are the same now as when Ultram was first approved, and the term "risk of discontinuation" refers to the risk of discontinuation for patients using the full non-titrated dosing, and that risk is also the same now as when Ultram was originally approved. As noted above, McNeil's 25 mg titration trial did not study either the benefits or the risks of full dosing, as referred to in the non-titrated dosing regimen, but rather only measured the rate of discontinuation using the 25 mg titration dosing as compared to a 10-day 50 mg titration schedule. As such, the 25 mg titration study is irrelevant to, and cannot possibly have been "essential to the approval" of, the risk-benefit language in the

[3] Available at www.fda.gov/ohrms/dockets/dailys/01/Oct01/102501/cp00001.pdf, at 73

non-exclusive non-titration dosing regimen. Accordingly that language is not eligible for exclusivity. *See* 21 U.S.C. § 355(j)(5)(D)(iv); 21 C.F.R. § 314.108(a).

Moreover, McNeil's position would require exclusivity to automatically extend to any and all changes included in an exclusivity supplement. This is contrary to law and more than a decade of FDA policy which only permit exclusivity for label changes for which "new clinical trials" were "essential to approval." 54 Fed. Reg. 28872, 28899 (July 10, 1989) ("under this provision...exclusivity would be provided only if 'new clinical investigations' were 'essential to approval' of the change.")(emphasis added)

Finally, if the quoted risk-benefit language (or the titration dosing schedule itself) is deemed by FDA to constitute safety-related or risk-related information that may not be carved out of Teva's labeling, that language is ineligible for exclusivity under longstanding FDA policy. McNeil concedes that FDA may properly preclude exclusivity for the types of labeling changes described in the 1994 preamble to FDA's final Hatch-Waxman regulations. *See* McNeil 5/31 Comments at 4, n. 2 ("It is true that the rule [citing to the preamble] precludes exclusivity for Warnings and other risk information ..."). As McNeil notes, this limitation includes, *by way of example*, warnings, but it also applies to "other similar **risk information that must be included in the labeling of generic competitors**." 59 Fed. Reg. 50338, 50356-57 (Final Rule, October 3, 1994) (emphasis added). Thus, if FDA agrees with McNeil's assertion that the risk-benefit language of the non-titration dosing schedule must be included in the labeling of Teva's tramadol product for safety reasons, that language is ineligible for exclusivity and may be used by Teva.

III. TEVA IS ENTITLED TO AN AB ORANGE BOOK RATING

McNeil argument. Teva's tramadol cannot be AB rated to Ultram due to "a different safety profile," and differences in dosage and administration. McNeil 5/31 Comments at 5.

Response: The Orange Book specifically permits AB ratings in situations such as this where there are "variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use." *See* Teva 5/23 Comments at 7-8. McNeil has offered no authority to rebut this conclusion.

IV. ULTRACET'S LABELING DISPROVES MCNEIL'S "RISK OF DISCONTINUANCE" ARGUMENT

McNeil argument: The Ultracet labeling's limitation to "short term (five days or less)" use provides "all of the necessary information to permit a physician to make an informed decision; the Teva label would be devoid of such information." McNeil 5/31 Comments at 5.

Response: The fact that the Ultracet labeling does not require titration and does not discuss any risks of discontinuation, shows that such "risk" is not sufficiently significant to block approval of a tramadol product labeled for use in patients for whom rapid pain relief is required. Teva's labeling, as well as Ultram's, permits non-titrated dosing under the same labeled conditions, for patients requiring rapid pain relief, and neither Ultram nor Teva's tramadol may

be dosed using a titration schedule for such patients. Thus, Teva's labeling is no more "devoid" of "necessary information" for non-titrated dosing than is Ultram's labeling.

CONCLUSION

McNeil's arguments are meritless and must be rejected by FDA. Teva's ANDA should be approved immediately.

Respectfully submitted,

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